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Running head: Methylphenidate for Hyperkinetic Disorder in Children with Intellectual Disability

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Randomized Controlled Double-Blind Trial of Optimal Dose Methylphenidate in Children and Adolescents with Severe Attention Deficit Hyperactivity Disorder and Intellectual Disability

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ABSTRACT (278 words)

Background: Attention deficit hyperactivity disorder is increased in children with intellectual disability. Previous research has suggested stimulants are less effective than in typically developing children but no studies have titrated medication for individual optimal dosing or tested the effects for longer than 4 weeks.

Method: 122 drug-free children aged 7-15 with hyperkinetic disorder and IQ 30-69 were recruited to a double blind, placebo-controlled trial that randomized participants using minimization by probability, stratified by referral source and IQ level in a one to one ratio. Methylphenidate was compared to placebo. Dose titration comprised at least one week each of low (0.5 mg/kg/day), medium (1.0 mg/kg/day) and high dose (1.5 mg/kg/day). Parent and teacher ADHD index of the Conners Rating Scale-Short Version at 16 weeks provided the primary outcome measures. Clinical response was determined with the Clinical Global Impressions scale (CGI-I). Adverse effects were evaluated by a parent-rated questionnaire, weight, pulse and blood pressure. Analyses were by intention-to treat.

Results: Methylphenidate was superior to placebo with effect sizes of 0.39 [95% confidence intervals (CIs) 0.09, 0.70] and 0.52 (95% CIs 0.23, 0.82) for the parent and teacher Conners ADHD index. Four (7%) children on placebo versus 24 (40%) of those on methylphenidate were judged improved or much improved on the CGI. IQ and autistic symptoms did not affect treatment efficacy. Active medication was associated with sleep difficulty, loss of appetite and weight loss but there were no significant differences in pulse or blood pressure.

Conclusions: Optimal dosing of methylphenidate is practical and effective in some children with hyperkinetic disorder and intellectual disability. Adverse effects typical of methylphenidate were seen and medication use may require close monitoring in this vulnerable group.

Keywords Attention Deficit Disorder with Hyperactivity; Randomized Controlled Trial ;
Autism; Mental Retardation; Intellectual Disability; Methylphenidate; Stimulants

Abbreviations: HSEN: Hyperactivity and Special Educational Needs Study

This trial is registered: International Standard Randomized Controlled Trial Number Register
(ISRCTN 68384912).

Attention deficit hyperactivity disorder (ADHD) and the more severe hyperkinetic disorder (HD) are characterized by levels of overactivity, inattention and impulsivity that are developmentally inappropriate and pervasive across different situations such as home, school and leisure activities. An association with subaverage intelligence is consistently identified; one epidemiological study reported an 8-fold increase in the rate of HD among children with global learning problems (Emerson, 2003) and another reported a 16-point decrease in IQ of those meeting a questionnaire algorithm for HD (Simonoff, Pickles, Wood, Gringras, and Chadwick, 2007). The latter study demonstrated that the psychiatric and cognitive correlates of HD were similar in those with IQ 40-69 compared to those of normal ability and showed both groups experienced similar psychosocial impact of HD.

Guidelines on medical management recommend methylphenidate as the first line (Pliszka, et al., 2006; Taylor, et al., 2004). The MTA trial demonstrated that individually titrated medication was significantly better than either treatment as usual (mostly medication), suggesting that individual dose selection is important in optimizing behavioural improvement (MTA Cooperative Group, 1999).

Most treatment trials for ADHD have excluded children with intellectual disability (ID) and the evidence pertaining to this group is restricted to a handful of studies. (Aman, Buican, and Arnold, 2003) aggregated the studies from his group, concluding that there was consistent evidence for a moderate effect size (0.57 for teachers, 0.39 for parents) but that this was considerably less than reported in studies with typically developing children, e.g., ~0.8-0.9 in the MTA titration trial (Greenhill, et al., 2001). Other groups (Handen, Feldman, Lurier, and Murray, 1999; Pearson, et al., 2003) consistently find similar moderate effects of methylphenidate. Aman's aggregated analysis further suggested that lower IQ/mental age predicted a poorer medication response. However, design limitations in all these studies affect the interpretation and resulting confidence in the evidence base. First, all recent studies were

crossover in design; the success of blinding was not consistently reported and there is often low power to detect order effects. Second, all trials were short-term in duration (2-4 weeks follow-up) and do not assess the medium- to long-term efficacy of ADHD treatment. Third, dosing regimens in some older trials did not follow current practice; all used immediate release formulation in twice rather than three times daily dosing and none used individual dose titration. Finally, sample sizes were very small (11-35 participants), producing imprecise estimates and not allowing tests of moderator effects. The latter are particularly important as both clinical reports (Campbell, 1978) and theoretical grounds (Barkley, McMurray, Edelbrock, and Robbins, 1992) suggest that those with autism may be particularly sensitive to adverse effects and prone to develop more tics, rituals/compulsions, stereotyped behaviours, irritability and social withdrawal (Handen, Johnson, and Lubetsky, 2000; Quintana, et al., 1995). A recent larger randomized controlled crossover trial in children with autism spectrum disorders (ASDs) and high levels of hyperactivity (Research Units on Pediatric Psychopharmacology (Autism Network), 2005) reported beneficial effects of stimulants amongst those tolerating medication but 13 of 72 (18%) withdrew due to adverse effects.

The present trial of immediate-release methylphenidate versus placebo in children with ID and hyperkinetic disorder aimed to answer the question, as set out in the protocol: (1) What is the efficacy and safety of stimulant medication over 16 weeks, under conditions of individual optimal dose titration; (2) What is the profile of adverse effects in this population; and (3) Is efficacy moderated by the level of ID, the presence of autistic symptoms or the severity of ADHD symptoms?

METHODS

This was a randomized controlled double-blind trial of immediate-release methylphenidate versus placebo individually titrated over 3 or more weeks followed by

optimal dose until 16 weeks post-randomization. Participants were allocated to treatments through the Mental Health and Neuroscience Clinical Trials Unit (CTU-London, UK). Allocation was undertaken independently of the trial team. The first 15 participants were allocated with simple randomisation. Thereafter, allocation was stratified by source of referral (clinical referral or community screening) and ID (full scale IQ score <50 or ≥ 50) with computer-generated probabilistic minimisation. Once notified by the CTU, the pharmacy dispensed the trial medication. An open-label phase (not described) followed the double-blind trial in which participants receiving placebo medication were offered active medication and those on active medication could continue methylphenidate treatment, including dose and formulation alternations. Ethical and regulatory approval was obtained from the Southeast Multi-Centre Research Ethics Committee (MREC +04/01/013) and Medicines and Healthcare Products Regulatory Authority (MHRA 8000/13629).

Participants were recruited through *clinical referrals* and *community screening* across the south-east of England and all assessments were completed by trial team members based at the Institute of Psychiatry. Paediatricians and child psychiatrists in the recruitment areas were informed of the trial and all clinical referrals were offered an eligibility assessment. Community screening employed two methods. In four health districts there was an up-to date Special Educational Needs Register, a database listing children requiring high levels of educational support; and children were identified whose difficulties suggested they might be eligible. Second, individual special schools for children with ID in the recruitment areas were individually approached. Screening employed the short form of the Conners Rating Scale (Conners, 1989); children were approached for an eligibility assessment if they received a Conners score (1) above the age-normed 90th centile on either parent ADHD index or hyperactivity scale and (2) above the 85th centile on either the teacher ADHD index or hyperactivity scale.

Participant inclusion criteria were: 7-15 years of age; a diagnosis of ICD-10 hyperkinetic disorder; and a full-scale IQ of 30-69. Diagnosis of hyperkinetic disorder was made using the Child and Adolescent Psychiatric Assessment (CAPA; Angold, et al., 1995) and details of implementation and IQ assessment are provided in the supplementary appendix. Symptoms of autism were measured with the parent-reported Social Communication Questionnaire (SCQ; Rutter, Bailey, and Lord, 2003) but the ICD-10 exclusion rule of an ASD was not employed. A psychiatric and medical history was undertaken at screening and each child received a physical examination. Further inclusion criteria were: living in a stable situation and regular school attendance. Exclusion criteria were: current stimulant use; use of neuroleptic medication in the last six months; history of a sensitivity reaction to stimulant medication; a diagnosis of a dementing disorder; epilepsy with daily seizures; presence of a psychotic, bipolar, severe obsessive-compulsive disorder or severe Tourette syndrome; or a household resident with a current substance abuse disorder. Only one child per family was enrolled in the double-blind phase at any one time. Written informed consent was obtained prior to randomization from parents/legal guardians of participants with assent of children as appropriate for their level of understanding.

Medication

Immediate-release methylphenidate supplied as Equasym[®] in 5, 10 and 20 mgs tablets comprised the active treatment; a matching placebo in identical 'doses' was manufactured by the Guy's and St. Thomas' Pharmaceutical Production Laboratory, which is approved by the UK MHRA.

Optimal dose titration and selection

This procedure aimed to assess participants on three daily doses: 0.5 (*low dose*). 1.0 (*medium*) and 1.5 (*high*) mgs/kg, given in increasing dose and delivered three times daily. At the end of titration, two senior medical investigators (ES, ET, GB and SB) independently

judged optimal dose for each participant using parent, teacher and clinician ratings on adverse events and behavioural improvement on the parent and teacher Conners ADHD index and hyperactivity scale. This dose was then prescribed for the remainder of the 16 week trial. (See supplementary appendix for details.)

Measures of efficacy

The primary outcome measures for this study were the parent and teacher Conners ADHD index at 16 weeks. Secondary outcome measures at 16 weeks included scores on the parent and teacher Conners hyperactivity scale and hyperactivity subscale of the Aberrant Behavior Checklist (ABC;). The Clinical Global Impressions-Improvement rating (CGI-I; Sharkey, 1985) was completed by the clinician with the parent at the 16-week assessment; ratings of ‘improved,’ ‘much improved’ and ‘completely recovered’ were categorized *post hoc* as a clinical response.

Safety

Possible adverse effects were monitored during dose titration and at the 8, 12 and 16 weeks post randomization visits, as described in the supplementary appendix. Because the optimal dosing design involved the trial of doses that may evoke short-term adverse effects, the primary interest was in adverse effects present at 16 weeks, on optimal dose, as measured by the parent questionnaire. Behaviours of *a priori* interest for individual analysis were: parent-rated sleep difficulties, poor appetite, looks sad/miserable, crying spells, looks anxious, meaningless repetitive behaviour and social withdrawal (talks less than usual with other children), with significant worsening classified as a two-point deterioration from baseline. In addition, two aggregate scores were calculated *post hoc*. The *target adverse effects score* summed the behaviours listed above and aimed to identify smaller differences across several adverse effects. The *other adverse effects score* comprised the other behaviours of the adverse effects questionnaire: stares a lot or daydreams; not interested in other children; irritable;

complains of stomach ache; complains of headache; drowsy; seems unsteady; excited; angry; has nightmares; displays twitches (tics); and shaking or tremor of hands. Changes in weight, pulse and blood pressure were also considered. We observed children who were withdrawn from medication because of adverse effects.

Statistical analysis

No formal interim analyses were performed. Sample size calculations were based on an effect size of 0.5 in the differential reduction in symptoms between baseline and 16 weeks (Research Units on Pediatric Psychopharmacology (Autism Network), 2005). A sample size of 64 per group gives 80% ($\alpha=0.05$, two-tailed) power. The analyses, using Stata version 11, followed a pre-specified plan and were performed on the intention-to-treat sample. Effect sizes were calculated as the estimated adjusted treatment effect divided by the pooled within group standard deviation of the outcome. Linear regression models were fitted for each outcome. All models included a fixed contrast for the treatment effect, the randomization stratification factors, age, sex, and baseline SCQ score. The screening and baseline values of the outcome were included as fixed covariates.

The moderator effects specified *a priori* were: severity of ID (baseline full-scale IQ), autistic symptoms (baseline SCQ score) and ADHD severity (baseline parent and teacher Conners ADHD index). Moderator analyses were performed on both primary outcomes by including an interaction between treatment and moderator and the results considered exploratory.

The adverse events measured on a continuous scale were examined using linear regression while binary events were examined using exact logistic regression, with contrasts for treatment, source and severity in each case. The two adverse effects scores were examined using separate regression analyses with contrasts for treatment, severity, source, gender and the covariates age and baseline SCQ. All other safety data are reported descriptively.

As a sensitivity analysis, the primary analyses were repeated including only *compliers* who took most or all medication doses as determined by parent and teacher report and clinician judgement. All statistical tests are two-sided.

Missing data were treated as missing at random and imputed using multiple imputation (Rubin, 1987) by chained equations (Van Buuren, Boshuizen, and Knook, 1999) using the *ice* package (version 1.1.4 (Royston, 2005)). The results of 200 imputed datasets were combined using Rubin's Rules (Rubin, 1987), implemented using the *mim* command (version 1.1.8 (Carlin, Galati, and Royston, 2008)). For the adverse events analysis, multiple imputation was not used.

Figure 1

RESULTS

We assessed 890 children (764 through community screening, 129 through clinical referral) for eligibility and 122 (73 community, 49 clinical) were randomized between June 2005 and July 2008. Participant characteristics by treatment group are shown in Table 1. Sixteen withdrew from the trial before week 16; 5 of the withdrawals, all on active medication, were due to adverse events (details in supplementary appendix). We followed 122 participants until 16 weeks and all are included in the intention-to-treat analysis. Eighty-seven (47 active, 40 placebo) were rated as having good or excellent medication compliance and are included in a sensitivity analysis. The doses being taken (including none for those withdrawn) are shown in the supplementary appendix.

Table 1

Behavioural Outcome

Table 3 shows that participants receiving active medication experienced a significantly greater reduction in parent- and teacher-rated symptoms on the Conners ADHD index.

Significant group differences were also seen for the parent and teacher Conners hyperactivity scale and the ABC hyperactivity scale. On the CGI-I, 24 of 61 (40%) participants receiving methylphenidate were rated as improved or better, compared to 4 of 57 (7.1%) of those on placebo, giving a number needed to treat (NNT) of 3. Sensitivity analysis including compliers only reported similar effect sizes to those seen in the intention to treat analysis (Table 2).

Table 2

Moderators of Response

None of the candidate moderators (IQ, autistic symptoms, parent- and teacher-rated ADHD severity) had an effect on parent- or teacher-rated Conners ADHD index at 16 weeks with p values ranging from .017 to .94.

Table 3

Adverse Effects

Children taking methylphenidate were more likely to have parent reports of sleep difficulties and poor appetite but the other parent-reported adverse events showed non-significant group differences (Table 3). There were no group differences in mean change in pulse or blood pressure. However, weight change from baseline differed significantly between groups (Table 4). The target adverse effects score decreased for both groups between baseline and week 16. There was a marginally-significant trend for the active treatment group to decrease less over the course of treatment. The other adverse effects score also showed a reduction for both groups between baseline and week 16 with no group difference.

Comparing the means and standard errors (SEs) of all 16 withdrawals (from both arms) to the non-withdrawals revealed a mean (SE) IQ of 51.8 (2.6) vs. 53.7 (1.0) and mean (SE) SCQ scores of 15.1 (1.9) vs. 17.4 (0.8), respectively. A similar comparison amongst only those receiving active medication and comparing the 5 withdrawn because of likely/definite

adverse effects vs. the 51 remaining on active medication revealed a mean (SE) IQ of 47.2 (4.7) vs. 54.1 (1.3) and SCQ scores of 18.4 (2.0) vs. 16.9 (1.1).

Table 4

CONCLUSIONS

Methylphenidate is effective in reducing ADHD symptoms in children with intellectual disability; the results reveal moderate effect sizes of 0.39-0.52 for the primary outcome of parent and teacher ADHD index. Some researchers have argued that the hyperactivity scale of the ABC is a more suitable measure for children with ID and it is interesting to note the parent (but not the teacher) effect size is larger and more consistent than seen for the Conners scales. However, the Conners scales provide comparability both to other studies of children with ID and also to the wider literature on children of average ability. A responder/non-responder classification using the CGI shows a highly significant ($p < .001$) group difference but this is partly driven by the relative absence of a placebo effect, with only 7% of those receiving placebo being responders. Other studies with a similar participant group have used a crossover design and placebo effects are largely unreported.

The present findings, including the effect sizes, are consistent with the previous literature. Aman's summary of the aggregated crossover trials of methylphenidate versus placebo, which reported a mean effect size of 0.57 for the four teacher-reported hyperactivity measures and 0.39 for the parallel parent scales (Aman, et al., 2003). However, because of the design differences in the present study, it cannot be inferred that the finding of similar effect sizes indicate that the use of individually titrated optimal three times daily dosing does not achieve better results than group-standardized, twice-daily dosing. Furthermore the trial end-point is significantly longer than that reported in previous trials.

This is the first trial to formally examine the role of treatment moderators such as IQ, autistic symptoms and ADHD severity. In the aggregate studies, Aman suggested that lower IQ/mental age might predict poorer treatment response. In our larger sample, we found no support for this. The studies aggregated by Aman included individuals with IQs up to 90 and it may be that the suggestive difference reported is due to greater response in those with IQ>70, rather than a difference among those in the ID range. The present finding of no subgroup difference according to autistic symptoms is in line with the findings in children with an ASD and high levels of hyperactivity, in which effect sizes for methylphenidate ranged from 0.20 to 0.54 (Research Units on Pediatric Psychopharmacology (Autism Network), 2005). Taken together, these two studies support the use of stimulant medication in children with combined ADHD and ASD symptoms. The current criteria do not allow the diagnoses of ADHD/hyperkinetic disorder when an ASD has been diagnosed. This is likely to change in the revisions of the DSM and ICD criteria and the current findings support this alteration in showing that children who likely meet both sets of criteria can benefit from stimulant treatment. We found that ADHD symptom severity did not predict response amongst those receiving a diagnosis of hyperkinetic disorder. In the present trial, 60% of the participants were not clinically recognized or treated for their ADHD symptoms; these findings suggest that clinicians should be more aware of the increased rate of ADHD among children with ID and the potential benefits of stimulant treatment, even amongst those with milder symptoms.

The rate of withdrawals, 13%, is similar to that reported in other studies of similar populations (Aman, Kern, McGhee, and Arnold, 1993; Research Units on Pediatric Psychopharmacology (Autism Network), 2005); furthermore, it should be noted that only 4% were withdrawn due to adverse effects. Nevertheless, treatment with methylphenidate produced significantly more adverse effects than seen with placebo. The adverse effects

profile was typical of methylphenidate, with sleep and appetite difficulties along with failure to gain weight. It is notable that these difficulties were seen even when participants were prescribed an optimally selected dose, in which acceptability of any adverse effects were considered. This highlights the need to regularly review adverse effects even when an initial dose has been carefully selected. However, it is interesting to note that the target adverse effects score decreased for both groups, indicating overall improvement, between baseline and week 16. Explanations for this include the fact that many adverse effects can also be indicators of comorbidity or alternatively that initial high scores show regression to the mean.

The current study has a number of strengths. The sample size is more than three times that of the next largest randomized double-blind study of methylphenidate in this population (Aman, et al., 1993). The larger sample size increases the precision of the effect size estimates and also allows the moderating effects of IQ, autistic symptoms and ADHD severity to be tested. The length of follow-up (16 weeks) is substantially longer than any other trial and therefore provides the first data on medium-term effects of medication. The study employed an intention to treat analysis and all but one participant was followed up until 16 weeks. All diagnoses of ADHD/hyperkinetic disorder were carefully considered using a research clinical instrument, the CAPA, as well as teacher Connors and direct behavioural observation; the combined information was reviewed in the context of participants' IQ results by at least one experienced clinician. The recruitment strategy included both clinically identified cases and also children in whom ADHD had not been previously recognized. Therefore the present findings are generalizable to the wider population of children with ADHD and ID. The dose optimization strategy employed in the current study was close to current clinical practice.

A potential limitation of the present study is the number of participants (33, 27%) with poor medication compliance. However, this proportion broadly reflects the experience in UK health care and should be considered a reflection of the representative nature of the sample. It

is interesting to note that the effect sizes from the sensitivity analysis that included only good compliers were similar to those from the full intention to treat analysis. Although the current trial is much larger than any previous study, the sample size is powered for the main effect of medication on ADHD symptoms and not for the moderating influences that were tested. Although the failure to identify any significant interaction must therefore be viewed with caution, it should also be noted that none of these effects approached significance. This suggests that any such moderating influence is likely to be subtle.

The study has three main findings. First, methylphenidate is effective in about 40% of children with hyperkinetic disorder and ID. Second, the adverse effects experienced by this population are similar to those seen in typically developing children with ADHD and can be identified with careful but routine monitoring of medication. The current study cannot exclude the presence of rare, atypical adverse events, but these apply to any population of children treated with medication. Nevertheless, because children with ID often have complicating medical problems and are less likely to be able to communicate subjectively experienced adverse events, particular care should be exercised in prescribing and monitoring stimulant medication. Finally, we found no evidence to support moderating effects of IQ, autistic symptoms or ADHD severity. Therefore, stimulants should be considered in children with hyperkinetic disorder and ID regardless of their profile with respect to these characteristics.

What is known

- ADHD and hyperkinetic disorder (HD) are increased about 8-fold in children with intellectual disability (ID) but often goes unrecognized
- Methylphenidate is the first line medication for children with ADHD/HD but the large, two-arm trials have excluded children with ID

What is new

- Treatment with methylphenidate was superior to placebo in reducing ADHD symptoms and producing clinical improvement
- Assessment of common adverse effects of insomnia, poor appetite and weight loss were associated with methylphenidate treatment but overall safety was good

What is clinically relevant

- ADHD/HD is important to identify and treat in children with ADHD/HD

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Table 1
Participant Baseline characteristics

Characteristic	Treatment Group		
	Overall (N=122)	Placebo (N=61)	Methylphenidate (N=61)
Type of referral (n, %clinical referral) ^a	73 (60)	36 (59)	37 (61)
Severity of intellectual disability (N, % IQ<50)	39 (32)	20 (33)	19 (31)
IQ (mean, SD) ^b	53(10.1)	53 (10.5)	54(9.6)
Age in months (mean, SD) ^c	134 (28)	138 (28)	130 (29)
Sex (N, % male) ^d	85 (70)	40 (66)	45 (74)
Type of school (N, % mainstream school) ^e	33 (27)	17 (28)	16 (26)
Teacher medication preference (N, % prefer active medication) (N=114)	32 (27)	16 (27)	16 (27)
Parent medication preference (N, % prefer active medication) ^f	91 (75)	48 (79)	43 (70)
Clinician medication preference (N, % prefer active medication) (N=117)	80 (66)	39 (67)	41 (69)
Parental education (n, % GCSE or lower qualification) (N=119) ^g	67(55)	30 (49)	37 (61)
SCQ (Mean, SD) (N=118) ^h	17.1 (8.0)	17.3 (8.7)	16.9 (7.3)
Parent Conners ADHD index (Mean, SD) (N=121) ⁱ	27.6 (5.9)	27.8 (5.1)	27.4 (6.6)
Teacher Conners ADHD index (Mean, SD) (N=120) ^j	20.6 (9.5)	19.7 (9.7)	21.5 (9.3)
Parent Conners hyperactivity scale (Mean, SD)	12.0 (3.8)	12.1 (3.7)	12.0 (4.0)

(N=121) ^k			
Teacher Conners hyperactivity scale (Mean, SD) (N=120) ^l	9.9 (5.9)	9.6 (5.8)	10.1 (6.0)
Parent ABC hyperactivity subscale (Mean, SD) (N=121) ^m	31.7 (9.2)	32.6 (9.7)	30.8 (8.7)
Teacher ABC hyperactivity subscale (Mean, SD) (N=121) ⁿ	21.2 (13.4)	20.5 (13.7)	21.9 (13.0)
Parental stress index (Mean, SD) (N=121) ^o	105.9 (22.0)	104.1 (20.1)	107.8 (23.8)
Weight (Kg) mean (SD) (N=121)	41.15 (17.5)	40.99 (14.9)	41.31 (19.9)
Blood pressure: Diastolic, mean (SD) (N=113)	66.6 (8.9)	67.0 (9.1)	66.2 (8.7)
Blood pressure: Systolic, mean (SD) (N=113)	103.1 (12.3)	103.2 (12.3)	103.4 (12.4)

a-g were included in the multiple imputations model.

h-o were pro-rated where there was less than 10% items missing. If there were more than 10% items missing, the scale score was recorded as missing.

h-o were included in the multiple imputations model after pro-rating.

Week 16 outcome values of i-o were included in the multiple imputation model as were screening values of i and j.

Treatment group and CGI-I score at week 16; and impact of childhood disability and Conners' symptoms score at baseline and week 16 were also included in the multiple imputation model.

Table 2
Effect of Treatment on Primary and Secondary ADHD Measures, Intention to Treat

	Methylphenidate		Placebo		Group difference	p-	Adjusted Effect
	Mean (se)		Mean (se)		in the mean	value	size–unadjusted SD
	Baseline	16 Weeks	Baseline	16 Weeks	difference		(95% CI)
					between the time-		
					points (95% CI)*		
<i>Intention to treat</i>							
Parent ADHD Index	27.4	19.1	27.8	22.4	-3.8	0.011	0.39
	(0.8)	(1.4)	(0.7)	(1.1)	(-6.7, -0.9)		(0.09, 0.70)
Teacher ADHD Index	21.5	14.5	20.0	18.6	-5.1	0.001	0.52
	(1.2)	(1.2)	(1.3)	(1.3)	(-7.9, -2.2)		(0.23, 0.82)
Parent Hyperactivity Scale	12.0	7.7	12.1	9.2	-1.8	0.03	0.33
	(0.5)	(0.7)	(0.5)	(0.7)	(-3.4, -0.2)		(0.03, 0.63)
Teacher Hyperactivity Scale	10.1	6.4	9.8	9.0	-3.2	<0.001	0.54
	(0.8)	(0.7)	(0.8)	(0.8)	(-4.9, -1.5)		(0.25, 0.82)
Parent ABC Hyperactivity Scale	31.0	20.6	32.6	28.7	-6.8	<0.001	0.56
	(1.1)	(1.6)	(1.2)	(1.6)	(-10.2, -3.5)		(0.29, 0.83)
Teacher ABC Hyperactivity Scale	21.8	13.2	20.5	18.1	-6.7	<0.001	0.54
	(1.7)	(1.5)	(1.8)	(1.7)	(-10.0, -3.3)		(0.26, 0.81)
<i>Compliers only</i>							

Parent ADHD Index	27.9 (0.9)	18.2 (1.6)	27.4 (0.8)	21.6 (1.4)	-3.40 (-6.89, -0.08)	0.055	0.33 (-0.01, 0.68)
Teacher ADHD Index	22.4 (1.3)	13.8 (1.3)	20.2 (1.6)	18.0 (1.8)	-5.83 (-9.32, -2.35)	0.001	0.57 (0.23, 0.91)
Parent Hyperactivity Scale	12.2 (0.6)	7.1 (0.8)	11.9 (0.6)	8.9 (0.8)	-1.91 (-3.76, -0.06)	0.043	0.36 (0.01, 0.72)
Teacher Hyperactivity Scale	10.8 (0.9)	6.1 (0.7)	9.9 (0.9)	8.7 (1.1)	-3.51 (-5.50, -1.52)	0.001	0.58 (0.25, 0.91)
Parent ABC Hyperactivity Scale	32.6 (1.2)	19.4 (1.8)	33.0 (1.4)	29.1 (1.9)	-8.77 (-12.58, -4.95)	<0.001	0.74 (0.42, 1.06)
Teacher ABC Hyperactivity Scale	22.5 (1.9)	12.3 (1.7)	21.9 (2.1)	18.5 (2.1)	-6.94 (-11.08, -2.80)	0.001	0.56 (0.22, 0.87)

* Group differences are adjusted for the randomisation factors, age, sex, baseline SCQ score, and the screening and baseline values of the outcome

Table 3
Individual adverse events at 16 weeks

	Number (%) of participants reporting significant increases		p-value
	Methylphenidate	Placebo	
Trouble getting to sleep	13 (21)	2 (3)	<0·01
Poor appetite	9 (15)	1 (2)	0·02
Looks sad/miserable	2 (3)	3 (5)	1
Crying	0	1 (2)	1
Looks anxious	2 (3)	1 (2)	0·99
Meaningless repetitive behavior	4 (7)	4 (7)	1
Talks less with other children	3 (5)	1 (2)	0·66

Table 4
Mean changes indicative of possible adverse events

	Methylphenidate		Placebo		Group difference in	p-value
	Mean (sd)		Mean (sd)		the mean difference	
	Baseline	Week 16	Baseline	Week 16	between the time- points (95% CI)*	
Weight ¹	41.3	39.6	41.0	43.8	-2.70	<0.001
	(19.9)	(17.3)	(14.9)	(16.8)	(-3.72, -1.67)	
Pulse ²	81.5	84.5	77.7	78.9	1.43	0.556
	(9.7)	(10.0)	(11.1)	(10.8)	(-3.38, 6.24)	
Systolic BP ³	103.0	104.2	103.2	102.1	3.11	0.213
	(12.4)	(11.5)	(12.3)	(12.1)	(-1.81, 8.02)	
Diastolic BP ⁴	66.2	67.6	67.0	64.4	3.29	0.131
	(8.7)	(9.8)	(9.1)	(9.4)	(-1.00, 7.58)	
Target adverse effects score ⁵	6.8	5.4	8.3	5.1	1.55	0.053
	(5.3)	(4.5)	(4.9)	(4.3)	(-0.02, 3.12)	
Other adverse effects score ⁶	10.1	6.5	11.2	7.9	-0.52	0.566
	(6.8)	(5.3)	(4.7)	(4.4)	(-2.32, 1.27)	

* Group differences for the continuous outcomes are adjusted for the randomisation factors

Group difference for the two adverse effects score are adjusted for gender, age and baseline SCQ

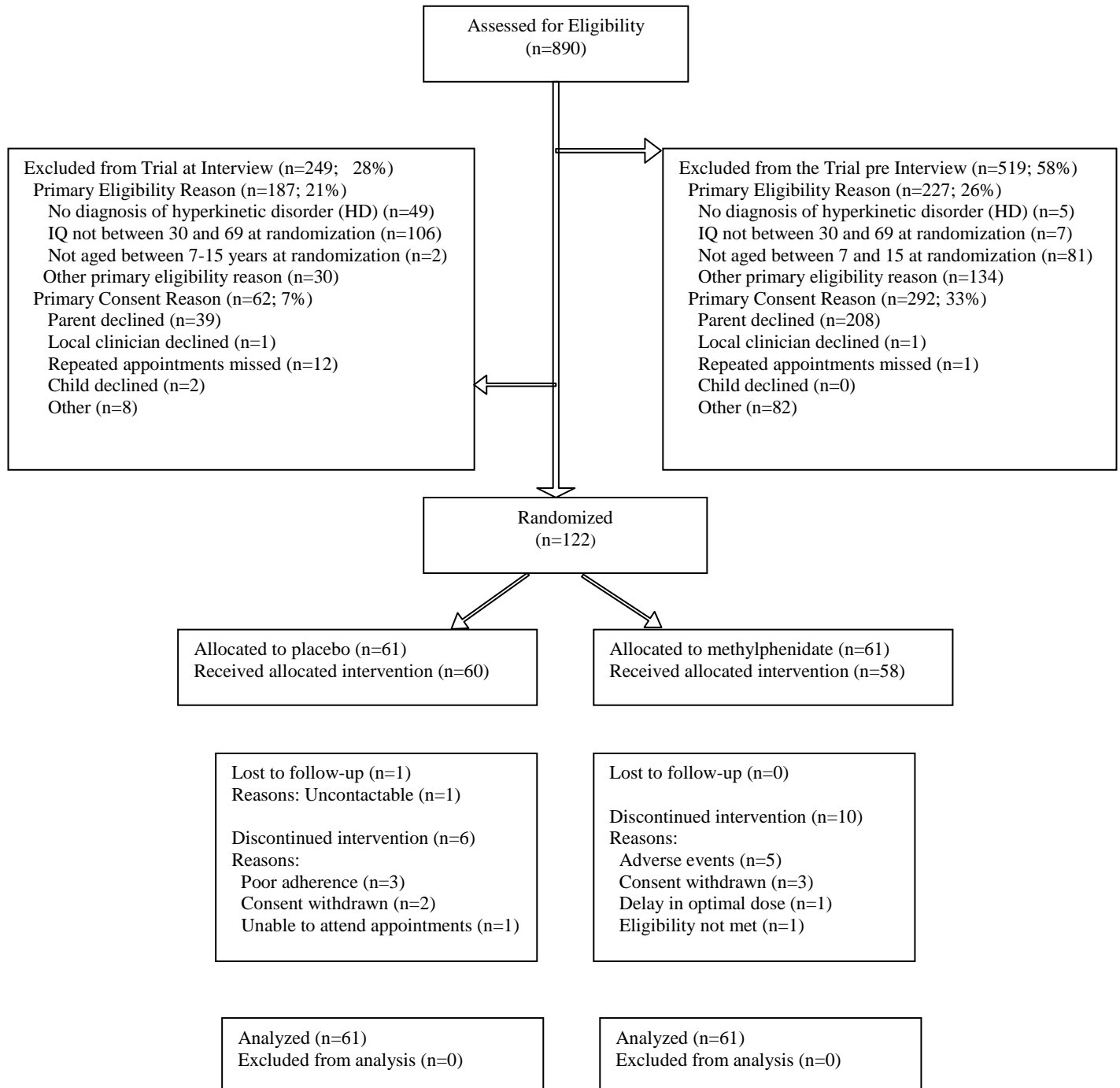
Missing data as follows:

1 Active group 2 at week 16; placebo group 1 at baseline, 4 at week 16

- 2 Active 4 at baseline, 7 at week 16; placebo 6 at baseline, 5 at week 16
- 3 Active 6 at baseline, 4 at week 16; placebo 3 at baseline, 6 at week 16
- 4 Active 6 at baseline, 4 at week 16; placebo 3 at baseline, 6 at week 16
- 5 Active group 1 at baseline, 2 at week 16; placebo 1 at week 16
- 6 Active 1 at baseline, 1 at week 16; placebo 2 at baseline, 1 at week 16

Figure 1

Diagram of participant selection and enrolment to the trial



SUPPLEMENTARY APPENDIX

Role of the Funding Source:

Study design, data collection, analysis and writing were fully independent of the funding body.

Screening for eligible participants

The purpose of screening with the parent and teacher short forms of the Conners rating scales was to identify children at risk for hyperkinetic disorder and intellectual disability. Previous research and clinical practice suggested this group of children are under-identified. Initially we set the age-related threshold for both parent and teacher ratings on either the ADHD index or hyperactivity scale at 90%. This was modified during the recruitment phase (by substantive amendment) to 85% for teacher ratings based on experience during the trial that a proportion of children meeting clinical research criteria for hyperkinetic disorder, described below, were falling under the 90% threshold on teacher ratings.

Psychiatric diagnosis

Hyperkinetic disorder was assessed by parental interview, undertaken by medical doctors in psychiatry and paediatrics, postgraduate research and clinical psychologists using the Child and Adolescent Psychiatric Assessment (CAPA; Angold, et al., 1995). The CAPA elicits behavioural accounts of hyperkinetic symptoms that were judged for their developmental appropriateness. In addition, psychologists recorded the child's behaviour during individual assessments of cognition and a free play/structured activities task designed to assess activity, attention and impulsivity with a descriptive commentary. Where teacher Conners ratings were at odds with parental accounts and researcher observations, a school observation was completed using a recording sheet to describe overactivity, inattention and impulsivity. A vignette using all sources of information described above was independently

rated for ICD-10 criteria by at least one senior investigator (ES), with a second opinion (ET, GB, SB, OC) in borderline cases. Mood and anxiety disorders were screened to ensure they did not account for the current symptom presentation. Autistic symptoms were quantified using the Social Communication Questionnaire (Rutter et al., 2003) but the exclusion was not applied.

Intellectual assessment

IQ was measured using the Wechsler Intelligence Scales for Children-IV (WISC-IV-UK (Wechsler, Rust, & Golombok, 2004), the Wechsler Preschool and Primary School Intelligence Scales (WPPSI-III; Wechsler, 2004)) or the Mullen Scale of Early Learning (Mullen, 1997), according to the child's age and estimated ability. Ratio IQs were employed when cognitive assessments were used out of age range (to avoid floor effects in participants of low ability).

Additional medical investigations

Children with a personal history of structural cardiac disease were cleared by a paediatric cardiologist; those with a history of early (<40 years) sudden death in a first degree family member had an electrocardiogram prior to enrolment.

Optimal dose titration

Prescribing was rounded to the nearest 5 mgs using a standardized table to indicate the doses and tablet strength according to the participant's weight. The total daily dose was divided so that 40% was given in the morning and at lunchtime and 20% after school. Variation in the timing of the after school dose was permitted according to personal needs and possible adverse effects. Participants received each dose, in order of low, medium, high, for at least one week during which they were attending school and physically well. Assessments during titration, used parent and teacher adverse effects ratings, reviewed personally by the medical doctor, to determine tolerability and safety of proceeding to the next dose. Although

parent and teacher Conners rating were obtained for optimal dose selection, these were not formally reviewed during titration. For optimal dose selection (undertaken blind to trial arm), each dose was first rated according to the acceptability of any possible adverse events. Amongst the doses judged acceptable, the one showing greatest behavioural improvement was selected as optimal. When no clinical difference between two doses could be identified, the higher dose was selected. Where senior investigators selected different doses, a consensus meeting was arranged and bringing in a third senior investigator if required.

Adverse effects

Parents and teachers completed a standard questionnaire on adverse effects (Hill & Taylor, 2001) augmented with additional symptoms seen in children with developmental disorders. Symptom ratings were on a 5-point scale (not at all, a few occasions only, about half the time, most of the time, all the time); these were compared with baseline ratings on the same scale. Clinical ratings of medication acceptability involved telephone interviews with parents at low dose and face-to-face parental interviews and physical examination at medium and high dose titration and at 8, 12 and 16 weeks post-randomization. During titration, an algorithm of number and severity of possible adverse events guided decisions about increasing dose.

For the analysis of adverse effects at 16 weeks, only the parent reports were used. This was decided upon *a priori* based on the observation during the titration phase that many teacher reports were inaccurate in their observation when followed up with a personal telephone call (e.g., describing stereotypies as tics).

Withdrawals due to adverse effects

There were 5 withdrawals due to adverse effects, all in the methylphenidate arm. These included, by participant: a combination of irritability, poor appetite and aggression; nausea and diarrhoea; blurred vision; urticaria; and irritability combined with social

withdrawal. An additional 11 children withdrew, 5 (3 active, 2 placebo) withdrawing consent after randomization, 3 (all placebo) due to poor medication adherence, 1 each because: eligibility criteria were not met on review (active arm); delay in reaching optimal dose (active); and failure to attend appointments (placebo).

Compliance

Compliance was rated at each visit by clinicians by asking parents how many doses the child had missed in the last week (the period under review for symptomatic improvement). In addition, the questionnaires sent to schools asked teachers to indicate whether the child had received all, some or none of the school day doses. This information was used to generate a rating of: all; most; some; few/no doses, completed at each assessment visit. Those for whom the rating at 16 weeks was most or all doses were considered *compliers*. Doses taken at 16 weeks are as follows:

Dose taken	Methylphenidate N (%)	Placebo N (%)
Low	8 (13.1%)	6 (9.8%)
Medium	14 (23.0%)	17 (27.9%)
High	28 (45.9%)	26 (42.6%)
None	11 (18.0%)	12 (18.6%)

where none includes whose optimal dose was selected as ‘none’ and those not taking medication regularly.